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CONTRACTING ORGANIZATION: University of Pennsylvania
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US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
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FORT DETRICK, MARYLAND 21702-5012

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ATTENTION OF:

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FOR THE COMMANDER:

PHYLLIS M. RINEHART
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13. ABSTRACT ***(Maximum 200 Words)***

This proposal is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol™. The recent discovery of two other natural products, epothilone and eleutherobin, that operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization, provides a unique opportunity for a collaborative approach using synthetic and computational studies for the elucidation of the pharmacophore common to these structurally dissimilar substances. Such an advance could lead to the development of a novel family of prostate cancer chemotherapeutics.

We describe herein our approach to the synthesis of novel analogs of the potent antitumor agent eleutherobin.

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FOREWORD

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12/22/99 _____ PI - Signature

Date

DAMD17-98-1-8547
Jeffrey D. Winkler, PI
Design and Synthesis of New Prostate Cancer Chemotherapeutic Agents

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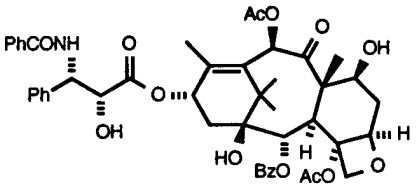
INTRODUCTION

This proposal is directed towards the development of new chemotherapeutic agents based on the mechanism of action of Taxol,™ 1. The recent discovery of two other natural products, epothilone 2, and eleutherobin 3, which operate by the same unique mechanism of action as Taxol™, i.e., microtubule stabilization, provides a unique opportunity for a collaborative approach to the elucidation of the pharmacophore common to these structurally dissimilar substances, using a combination of synthetic and computational studies. Such an advance could lead to the development of a novel family of prostate cancer chemotherapeutics.



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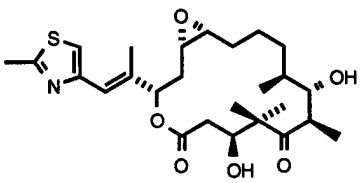

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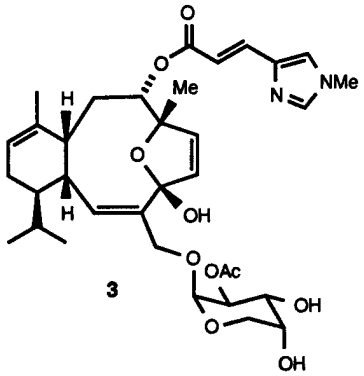

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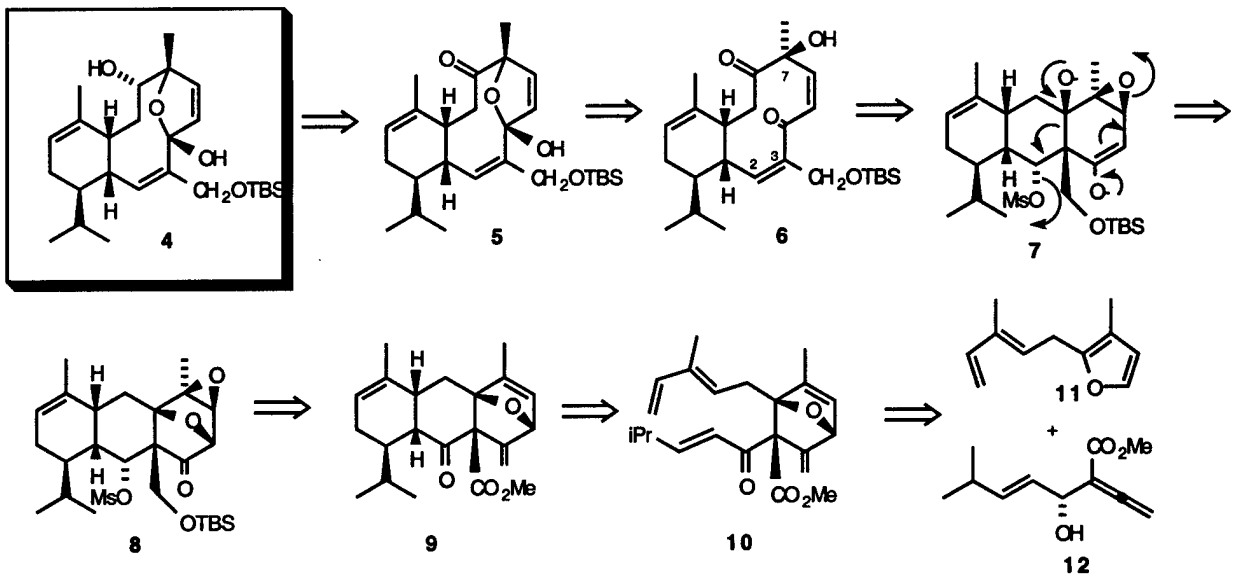
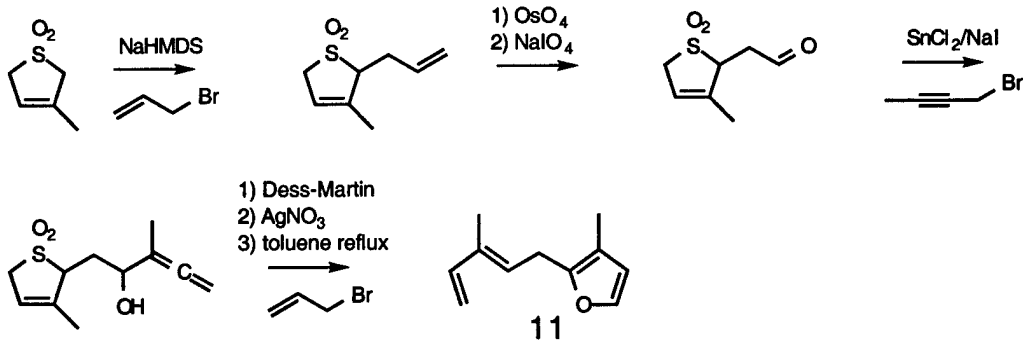
BODY

The recent discovery that eleutherobin is the most biologically potent of the three aforementioned natural product classes has prompted us to pursue the synthesis of eleutherobin

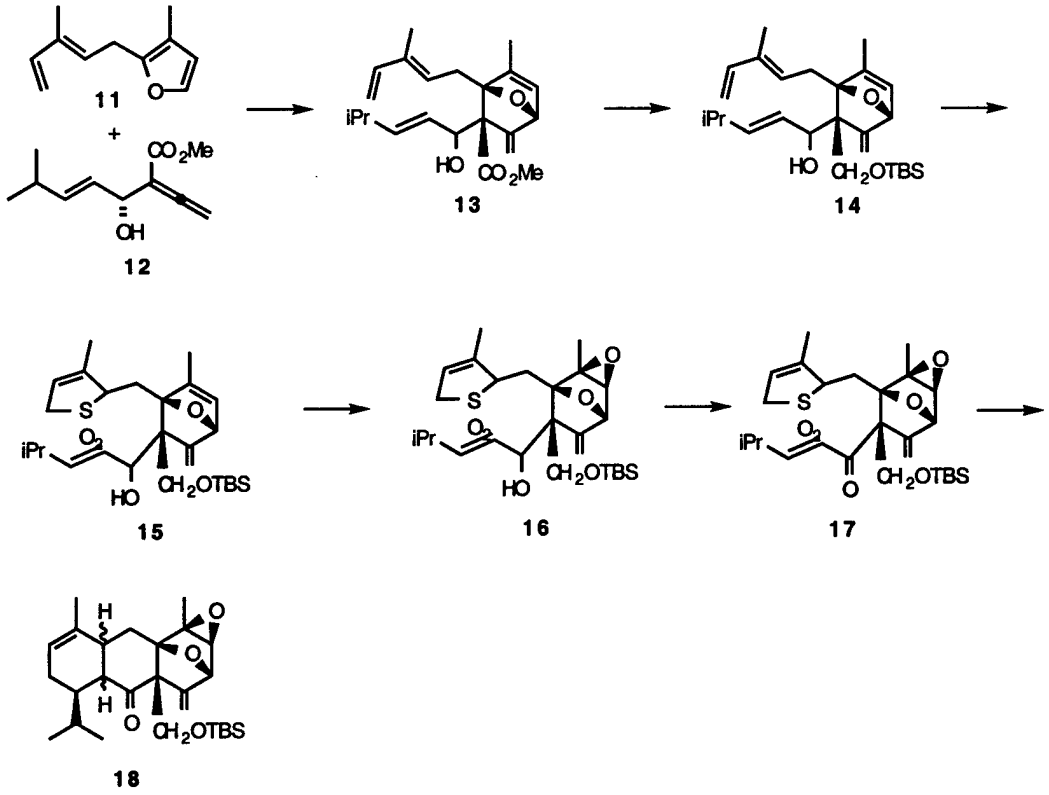


for the same SAR studies that we outlined originally for epothilone. The retrosynthetic analysis for our proposed construction of eleutherobin is outlined in the Scheme above.

Significant progress has been achieved in realizing the proposed scheme. First, we have developed a highly efficient approach to the synthesis of the key bis-diene moiety 11 as outlined below.



Second, we have established the viability of both the inter- and intramolecular cycloaddition reactions outlined in the retrosynthetic scheme. As shown below, the synthesis of the pentacyclic compound 18 (the silyl ether corresponding to the ester 9 in the retrosynthesis) has been achieved, although the stereochemistry of 18 has not yet been fully determined.



As described in the original application, we are continued our modeling studies in an effort to establish a general method for the establishment of the pharmacophore for structurally dissimilar ligands when the structure of the binding site is not known.

Relevance to the Original Hypothesis: Significant progress has been achieved in the efficient synthesis of a highly potent microtubule binding natural product, eleutherobin.

KEY RESEARCH ACCOMPLISHMENTS:

* A highly efficient synthesis of the bis-diene moiety has been developed
* Preliminary results indicate that the key Diels-Alder methodology works well and leads to an efficient synthesis of the key intermediate 18 for the fragmentation studies; and
* Work is underway to develop a general method for the identification of pharmacophores of structurally dissimilar substances using the RigFit program.

REPORTABLE OUTCOMES:

A publication is in preparation describing the synthesis of the bis-diene and the preparation of the pentacyclic intermediate 18.

CONCLUSIONS:

We have established that the proposed retrosynthetic scheme leads to an efficient preparation of the key intermediate for the proposed fragmentation approach to the synthesis of eleutherobin, a potent microtuble binding antimitotic. If the fragmentation reaction works well, this will result in an important improvement in the laboratory synthesis of this scarce natural product, facilitating the preparation of analogs for SAR studies. The ultimate goal of this work is to develop new drugs for prostate cancer based on these taxol-like substances.

APPENDIX:

A current cv for the PI.

CURRICULUM VITAE

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University of Pennsylvania
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BIRTH DATE: April 14, 1956

EDUCATION:

Post-doctoral: Columbia University. January 1982-August 1983.
Research Director: Professor Ronald Breslow.

Graduate: Columbia University. September 1977-December 1981.
M.A. 1978, M.Phil., Ph.D. 1981.
Thesis Advisor: Professor Gilbert Stork.

Undergraduate: Harvard College. September 1973-June 1977.
A. B. cum laude in Chemistry, 1977.

PROFESSIONAL EXPERIENCE: Professor, University of Pennsylvania
Department of Chemistry, July 1996-

Founding Member, University of Pennsylvania
Center for Cancer Pharmacology, May 1998-present

Associate Professor, University of Pennsylvania,
Department of Chemistry, July 1990-June 1996
Member, University of Pennsylvania Cancer Center,
July 1993-present

Assistant Professor, University of Chicago,
Department of Chemistry, September 1983-June 1990

AWARDS & HONORS: American Chemical Society Cope Scholar Award, 2000
Parke-Davis Lecturer, Michigan State University, 2000
Chairman, Philadelphia Organic Chemists' Club, 1995
H. Martin Friedmann Lecturer, Rutgers University, 1993
American Cyanamid Young Faculty Award, 1989-1992
NIH-NCI Research Career Development Award, 1988-1993
Alfred P. Sloan Research Fellow, 1987-1989
Merck Foundation Award for Faculty Development, 1985
American Cancer Society Postdoctoral Fellow, 1982-1983

RESEARCH SUPPORT

ACTIVE

CA 40250-08A2 (Winkler) 2/5/98-12/31/00 20%
National Institutes of Health $191,555 (direct costs/year)
Strategies for the Synthesis of Antitumor Compounds
This proposal is directed towards the development of new approaches to the construction of the naturally occurring substances manzamine and ingenol.

N-00014-93-1-0836 (Winkler) 10/1/95-9/30/99 5%
Office of Naval Research $85,513 (direct costs/year)
Binding and Transport of Metal Ions
This proposal is directed towards the development of immobilized and fluorescent systems for the development of metal ion sensors for use in the marine environment.

BCRP-971965 (Winkler) 7/15/98-7/14/01 20%
DOD Breast Cancer Research Program (IDEA) $69,905 (direct costs/year)
Design and Synthesis of New Breast Cancer Chemotherapeutic Agents
This proposal is directed towards design and synthesis of new breast cancer chemotherapeutic agents based on taxol and epothilone. The synthetic work in this proposal is directed towards the synthesis of bicyclic analogs of epothilone

PRF-AC (33255) (Winkler) 9/01/98-8/31/00 5%
Petroleum Research Fund $30,000 (direct costs/year)
Novel Chemical Systems Based on Spiropyran Indolines
This proposal is directed towards the development of spiropyrans as control mechanisms for the design and synthesis of gating mechanisms for signal transduction, a critical component in the construction of molecular devices.

PC970475 (Winkler) 9/1/98-2/28/0120%
DOD Prostate Cancer Research Program $114,960 (direct costs/year)
Design and Synthesis of New Prostate Cancer Chemotherapeutic Agents
This proposal is directed towards design and synthesis of new prostate cancer chemotherapeutic agents based on taxol and epothilone. The synthetic work in the DOD PC grant is directed towards the synthesis of the left- and right-hand halves of an X-ray based bridged bicylic analog of epothilone

Boehringer Ingelheim 1/1/99-12/31/99 (0%)
Synthesis of α -Methyl-α-Amino Acids $37,670 (direct costs/year)
This proposal involves support for one postdoctoral on a project that is directed towards a novel approach to the synthesis of amino acids.

PROFESSIONAL ACTIVITIES

Consultant, Wyeth-Ayerst Pharmaceuticals (1998-)
Associate Editor, *Organic Letters* (1999-)

INVITED LECTURES SINCE 1990:

Merck, Sharp & Dohme (West Point, PA)
Smith, Kline and Beckmann
Invited Lecturer, Symposium on Organic Synthesis, Great Lakes Regional ACS Meeting, Dekalb, Illinois Invited Lecturer, Molecular Recognition Meeting, Office of Naval Research, Charleston, S.C
Invited Lecturer, Symposium on Heterocyclic Chemistry, National ACS Meeting, Washington, D.C
Squibb Institute for Medical Research (Princeton, NJ)
University of Rochester
Squibb Institute for Medical Research (New Brunswick, NJ)
Boehringer-Ingelheim Pharmaceuticals
Brandeis University
University of Delaware
ICI Pharmaceuticals
New York Academy of Sciences
North Jersey ACS Meeting
Invited Lecture, 1992 Meeting of the American Society for Photobiology
Organizer and Lecturer, Symposium on Studies Toward the Total Synthesis of Taxol, National ACS Meeting, San Francisco, CA. (April 8, 1992)
Dupont Agricultural Products
Burroughs Wellcome
University of Virginia
Sandoz Institute
Sterling Winthrop
Bryn Mawr College
Invited Lecturer, Symposium on Organic Chemistry, Great Lakes Regional ACS Meeting, Ann Arbor, Michigan
Invited Lecturer, Symposium on Organic Synthesis, Middle Atlantic Regional ACS Meeting, Baltimore, Maryland
Technion-Israel Institute of Technology
Pfizer Central Research
Sandoz Institute
Hebrew University of Jerusalem
R. W. Johnson
University of Montreal
Plenary Lecturer, Wyeth-Ayerst Fourth Annual Chemical Sciences Symposium
Merck (West Point, PA)
American Cyanamid
Rhone-Poulenc Agricultural
Plenary Lecture, Interamerican Photochemical Society
University of Maryland
R. W. Johnson Pharmaceutical Research
Wyeth-Ayerst

Sepracor
Boehringer-Ingelheim
Florida State University
Northwestern University
UCLA
University of Minnesota
Parke-Davis
Pfizer
Penn State University
Smith Kline Beecham
Temple University
Amgen
University of Chicago
Dupont Pharmaceuticals
Invited Speaker, Symposium on Solid Support Chemistry, Middle Atlantic Regional ACS Meeting, May 1999
Plenary Lecturer, Symposium on Heterocycles, Canadian Institute of Chemistry, June 1999
Invited Speaker, Gordon Conference on Heterocycles, July 2000
University of Western Ontario
Boehringer-Ingelheim, Montreal
Michigan State University

PUBLICATIONS :

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2. G. Stork, C. Shiner, J. Winkler, "Stereochemical Control of the Internal Michael Reaction. A New Construction of trans-Hydrindane Systems," *J. Am. Chem. Soc.* **1982**, *104*, 310-312.

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13. J. Winkler, K. Deshayes, "Photodynamic Macrocycles," *J. Am. Chem. Soc.* **1987**, *109*, 2190-2191.

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